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Review

Genus *Ilex* L.: Phytochemistry, Ethnopharmacology, and Pharmacology

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ABSTRACT

The genus *Ilex* L. has been used as remedies in traditional Chinese medicine in Aquifoliaceae and beverages for thousands of years due to abundant pharmaceutical bioactivities. There are 600 species in genus *Ilex* L. containing various compounds such as terpenoids, saponins, glycosides, etc. Three species, *I. cornuta*, *I. chinensis*, and *I. rotunda* have been admitted in *Chinese Pharmacopoeia 2015* to treat dyspepsia, stomatitis, and hyperactivity cough and protect the liver and kidney. Recent studies showed that several species have been daily drunk to promote human health and prevent cardiovascular diseases in the folk. Here we reviewed the genus *Ilex* L. in phytochemistry, ethnopharmacology, and pharmacology.

Key words
Aquifoliaceae; ethnopharmacology; *Ilex* L.; pharmacology; phytochemistry; traditional Chinese medicines

1. Introduction

The genus *Ilex* L. is the only living genus in the family of Aquifoliaceae including about 600 species, mainly spreading in North and South America, tropical and temperate Asia and dotted in Europe and Oceania (Manen et al, 2010). It grows in forms of trees, climbers, and shrubs. China is one of the major countries in *Ilex* L. plant resources, of which 200 species distribute largely in southern China, e.g., Guangdong, Yunnan, Hunan, and Zhejiang provinces (Peng et al, 2013).

More than 40 species and their varieties are used for the medicinal purpose, in which *Ilex chinensis* Sims, *I. cornuta* Lindl., *I. rotunda* Thunb., *I. cornuta* Lindl., *I. pernyi* Franch., and *I. pubescens* Hook are botanical resources of crude drugs (Committee of Chinese Herbacology, 2004) in China, and the first three species were recorded in *Chinese Pharmacopoeia 2015* (Pharmacopoeia Committee of P R. China, 2015). They are remedies for clearing heat, moistening the lung, removing phlegm, invigorating the liver and lung in traditional Chinese medicine (TCM), and they are also jointly used with other herbs in Chinese patent drugs (Table 1). In addition, several species are used as non-*Camellia* teas due to belong non-*Camellia* species (Han et al, 2013). For example, *I. latifolia* Thunb., *I. kudingcha* C. J. Tseng (Large-leaved Kudingcha), *I. paraguariensis* A. St.-Hil. (Yerba Mate), and *I. vomitoria* Sol. ex Aiton (Yaupon) have being daily drunk to promote human health and prevent cardiovascular diseases in folk of southern China and Western countries especially in North and South of America, e.g. US, Paraguay, Peru, Ecuador, and Brazil for thousands of years.

In the 21th century, there have been great changes in human disease spectrum: increasing people are suffering from modern civilization diseases such as cardiovascular diseases, cancer, and diabetes and excessive increase in medical costs (Samocha et al, 2014). The experiences of traditional therapy show that species in the genus *Ilex* L. are potential remedies for the modern diseases. Here we reviewed the genus *Ilex* L. in phytochemistry, ethnopharmacology, and pharmacology (Figure 1).

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Table 1 Formula containing medicinal species from genus *Ilex* L.

Drugs	Herbs	Efficiency and diseases
Compound Maodonqing and Aluminium Clofibrate Tablets	***Ilicis Pubescentis Radix*** (*I. pubescens*), vitamin C, vitamin B6, inositol, chlorobenzene butyl aluminum, lecithin	Clearing heat and removing toxicity, activating blood and dredge the meridians. To treat coronary atherosclerosis heart disease
Compound Tiedongqin Pills	***Ilicis Rotundae Cortex*** (*I. rotunda*), *Taraxaci Herba*, *Paeoniae Rubra Radix*, Chinese Honeylocust Spine, *Chuanxiong Rhizoma*, Carthami Flos, *Angelicae Sinensis Radix*	Clearing heat and removing toxicity, promoting diuresis and alleviating pain. To treat pelvic inflammatory disease
Compound Sijiqin Pills	***Ilicis Chinensis Folium*** (*I. chinensis*), *Lonicerae Confusae Flos*	Clearing heat and removing toxicity, resolving swelling and dissipating blood stasis. To treat cough caused by lung-heat, sore throat, dysentery, hypochondriac pain, heat stranguria; skin ulcer, burns and scalds
Shiliuwei Dongqing Pills	***Ilicis Chinensis Folium*** (*I. chinensis*), *Cinnamomi Cortex*, *Amomi Rotundus Fructus*, *Caryophylli Flos*, *Aucklandiae Radix*, *Glycyrrhizae Radix*, *Aquilariae Resinatum Lignum*, *Bistortae Rhizoma*, *Piperis Longi Fructus*, *Myristicae Semen*, European Grape Fruit, *Carthami Flos*, *Choerospondiatis Fructus*	Clearing heat and removing toxicity, resolving swelling and dissipating blood stasis. To treat edmea, cold cough, dizziness
Compound Jiubiying Capsules	***Ilicis Rotundae Cortex*** (*I. rotunda*), *Atalantiae Buxifoliae Radix*, *Cyperi Rhizoma*	Clearing heat-toxin, inducing diuresis. To treat diarrhea, gastroenteritis

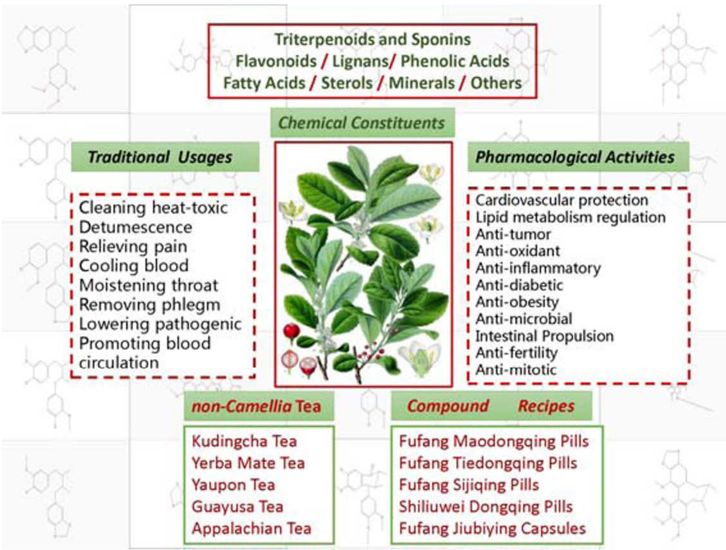

Figure 1 Chemical components, ethnopharmacology, and pharmacology of plants from *Ilex* L.

2. Phytochemistry of plants in *Ilex* L.

More than 200 compounds have been isolated and identified from the plants of *Ilex* L., including triterpenoids, triterpenoid saponins, flavonoids, sterols, polyphenols, carboxylic acids, and esters. The dominant constituents are triterpenoids and their saponins responsible for the modulation of lipid metabolism activities, anti-obesity, anti-inflammatory, and anti-microbial bioactivities (Table 2). Over the past 30 years, phytochemistry studies have been intensively carried out upon *I. chinensis*, *I. rotunda*, *I. cornuta*, *I. latifolia*, *I. purpurea*, *I. asprella*, and *I. pernyi*.

2.1 Triterpenoids and triterpenoid saponins

A total of 180 triterpenoids and triterpenoid saponins have been isolated and identified from the plants of *Ilex* L. According to chemical diversity of carbocyclics, triterpenoids are classified into acyclic triterpenoid, tricyclic triterpenoid, tetracyclic triterpenoid, and pentacyclic triterpenoid, in which pentacyclic triterpenoids are the dominant that includes lupane pentacyclic triterpenoids, oleanane pentacyclic triterpenoids, and ursane pentacyclic triterpenoids. They are mainly present in the leaves, barks, and root barks of plants in *Ilex* L. instead of other genera.

Table 2 Chemical constituents in plants of *Ilex* L.

	Compounds	Botanical resources	Parts of plants	References
Lupane pentacyclic triterpenoids				
1	Ilexoside A	*I. chinensis*	leaves	Cai et al, 2010
2	Ilexoside B	*I. asprella*	roots	Lee et al, 2015
		I. chinensis	leaves	Cai et al, 2010
3	Ilexoside C	*I. crenata*	fruits	Kakuno et al, 1991
4	Ilexoside D	*I. pubescens*	roots	Jiang et al, 2005
		I. kudingcha	roots	Huang et al, 2015
5	Ilexoside E	*I. crenata*	fruits	Kakuno et al, 1991
6	Ilexoside F	*I. crenata*	fruits	Kakuno et al, 1991
7	Ilexoside G	*I. crenata*	fruits	Kakuno et al, 1991
8	Ilexoside H	*I. crenata*	fruits	Kakuno et al, 1991
9	Lupeol	*I. centrochinensis*	leaves and roots	Wen and Chen, 1996
		I. cornuta	leaves	Che et al, 2011
		I. latifolia	leaves	Heck et al, 2008
10	Lup-20(29)-ene-3β-,24-diol	*I. latifolia*	leaves	Wu et al, 2008
11	3β-hydroxy-20-oxo-30-norlupane	*I. cornuta*	leaves	Qin et al, 1986
12	30-oxolupeol	*I. cornuta*	leaves	Nakanishi et al, 1982
13	Betulonic acid	*I. cornuta*	roots	Yang and Yan, 2002
14	Aculeoside I	*I. buxifolia*	leaves	Taketa et al, 2004b
Oleanane pentacyclic triterpenoids				
15	Asprellic A	*I. asprella*	leaves	Zheng et al, 2014
16	Asprellic B	*I. asprella*	leaves	Zheng et al, 2014
17	Asprellic C	*I. asprella*	leaves	Bai et al, 2011
18	Calenduloside E	*I. pubescens*	roots	Chen et al, 2011
19	Cornutaside C	*I. cornuta*	leaves	Li et al, 2006
20	Cornutaside D	*I. cornuta*	leaves	Li et al, 2006
21	Oleanolic acid	*I. centrochinensis*	leaves and roots	Gau et al, 1983
		I. asprella	leaves	Wang et al, 2009
22	Pedunculoside	*I. rotunda*	root barks	Gau et al, 1983
		I. cornuta	leaves	Fan et al, 2013
		I. chinensis	leaves	Cai et al, 2010
		I. pubescens	roots	Ren et al, 2011
23	Latifoloside G	*I. latifolia*	leaves	Ouyang et al, 1998
24	Latifoloside H	*I. latifolia*	leaves	Ouyang et al, 1998
25	Latifoloside Q	*I. latifolia*	leaves	Ouyang et al, 2001
26	Sapanin E6	*I. buxifolia*	leaves	Huang et al, 2001
27	Siaresinolic acid	*I. asprella*	roots	Fan et al, 2013
28	Hede-ragenin	*I. cornuta*	roots	Fan et al, 2013
29	Ilexolic acid B	*I. rotunda*	leaves	Wang et al, 2013
30	Ilexoside L	*I. rotunda*	leaves	Wang et al, 2013
31	Ilexoside LI	*I. rotunda*	leaves	Wang et al, 2013
32	Ilexkudinoside O	*I. latifolia*	leaves	Fan et al, 2013
33	Ilexoside XLIX	*I. rotunda*	leaves	Nakatani et al, 1989
34	Ilexoside XLVI	*I. rotunda*	leaves	Nakatani et al, 1989
35	Ilexoside XLVII	*I. rotunda*	leaves	Nakatani et al, 1989
36	Ilexoside XLVIII	*I. rotunda*	leaves	Nakatani et al, 1989
37	Ilexoside XV	*I. crenata*	root barks	Amimoto et al, 1993a
38	Ilexoside XVI	*I. crenata*	root barks	Amimoto et al, 1993a
39	Ilexoside XVII	*I. crenata*	root barks	Amimoto et al, 1993a
40	Ilexoside XX	*I. crenata*	root barks	Amimoto et al, 1993a
41	Ilexoside XXVI	*I. crenata*	root barks	Amimoto et al, 1993a
42	Ilexoside XXXII	*I. rotunda*	leaves	Nakatani et al, 1989
43	Ilexoside XXXIII	*I. rotunda*	leaves	Nakatani et al, 1989
44	3β-*O*-β-*D*-glucopyranosyl-(1→2)-α-*L*-arabi nopyranosyl-oleanolic acid	*I. bxifolia*	leaves	

To be continued

Continued Table 2

	Compounds	Botanical resources	Parts of plants	References
45	3-*O*-α-*L*-arabinopyranosyl pomolic acid	*I. asprella*	roots	Wang et al, 2009
46	3-*O*-β-*D*-glucopyranosyl(1→2)-β-*D*-[6-*O*-methyl-glucuronopyranosyl]-oleanolic acid-(28→1)-*O*-β-*D*-glucopyranosyl ester	*I. chinensis*	leaves	
47	3-*O*-β-*D*-xylopyranosyl spathodic acid 28-β-*D*-glucopy ranosyl ester	*I. pubescens*	roots	Ren et al, 2011
48	3β-[(α-*L*-arabinopyranosyl)oxy]-19α-hydroxyolean-12-en-28-oic acid 28-*O*-β-*D*- glucopyranosyl ester	*I. rotunda* *I. amara*	root barks leaves	Nakatani et al, 1989
49	3β-hydroxy-20-oxo-30-norlupane	*I. cornuta*	leaves	Nakatani et al, 1989
50	11-keto-α-amyrin palmitate	*I. cornuta*	leaves	Nakatani et al, 1989
51	23-hydroxy-oleanolic acid	*I. latifolia*	leaves	Ouyang et al, 2001
52	3-*O*-β-*D*-glucopyranosyl-(1→2)-β-*D*-[6-*O*-methyl-glucuronopyranosyl]-oleanolic acid-(28-1)-*O*-β-*D*-glucopyranosyl ester	*I. buxifolia*	leaves	Zhou et al, 2013a
53	3β-*O*-[β-*D*-glucopyranoside-(1→3)]-[α-*L*-rhamnopyranosyl(1→2)]α-*L*-arabinopyranosylolean	*I. chinensis*	leaves	Zhou et al, 2013a
54	3β-*O*-β-*D*-glucopyranosyl-(1→3)-α-*L*-2-*O*-acetylarabinopyranosylolean-12-en-28-oic acid-28-*O*-β-*D*-glucopyranosylester	*I. amara*	leaves	Zhou et al, 2013a
55	2α,3β,19α,23-tetrahydroxy-ursolic acid-12-en-28-oic-28-β-*D*-glucopyranoside	*I. litseaefolia*	leaves	Zhou et al, 2013a
Ursane pentacyclic triterpenoids				
56	Cornutaside A	*I. cornuta*	leaves	Zuo et al, 2011
57	Cornutaside B	*I. cornuta*	leaves	Zuo et al, 2011
58	Cornutaside C	*I. cornuta*	leaves	Zuo et al, 2011
59	Cornutaside D	*I. cornuta*	leaves	Zuo et al, 2011
60	Matesaponin 1	*I. paraguariensis*	leaves	De Souza et al, 2011
61	Matesaponin 2	*I. paraguariensis*	leaves	De Souza et al, 2011
62	Matesaponin 3	*I. paraguariensis*	leaves	De Souza et al, 2011
63	Matesaponin 4	*I. paraguariensis*	leaves	De Souza et al, 2011
64	Ilexsaponin A	*I. pubescens* *I. hainanensis*	roots and stems leaves	Li et al, 2014a Zhou et al, 2007
65	Ilexsaponin B	*I. pubescens*	roots	Li et al, 2014a
66	Ilexsaponin B1	*I. pubescens*	roots and stems	Li et al, 2014a
67	Ilexsaponin B2	*I. pubescens*	roots and stems	Li et al, 2014a
68	Ilexsaponin B3	*I. pubescens*	roots	Li et al, 2014a
69	Ilexkudinoside H	*I. rotunda*	root barks	Amimoto et al, 1993b
70	Ilexkudinoside I	*I. kudingcha*	leaves	Ouyang et al, 1996
71	Ilexkudinoside J	*I. kudingcha*	leaves	Ouyang et al, 1996
72	Ilexkudinoside K	*I. kudingcha*	leaves	Ouyang et al, 1996
73	Ilexkudinoside L	*I. kudingcha*	leaves	Ouyang et al, 1996
74	Ilexkudinoside M	*I. kudingcha*	leaves	Ouyang et al, 1996
75	Ilexkudinoside N	*I. latifolia*	leaves	Ouyang et al, 1998
76	Ilexkudinoside O	*I. latifolia*	leaves	Ouyang et al, 1998
77	Ilexkudinoside P	*I. kudingcha*	leaves	Ouyang et al, 1996
78	Ilexkudinoside Q	*I. kudingcha*	leaves	Ouyang et al, 1996
79	Ilexkudinoside R	*I. kudingcha*	leaves	Ouyang et al, 1996
80	Ilexkudinoside S	*I. kudingcha*	leaves	Ouyang et al, 1996
81	Latifoloside I	*I. latifolia*	leaves	Huang et al, 2001
82	Latifoloside J	*I. latifolia*	leaves	Huang et al, 2001
83	Latifoloside K	*I. latifolia*	leaves	Huang et al, 2001
84	Latifoloside L	*I. latifolia*	leaves	Huang et al, 2001

To be continued

Continued Table 2

	Compounds	Botanical resources	Parts of plants	References
85	Gouguside 1	*I. cornuta*	leaves	Liao et al, 2013
86	Gouguside 2	*I. cornuta*	leaves	Liao et al, 2013
87	Gouguside 3	*I. cornuta*	leaves	Liao et al, 2013
88	Gouguside 4	*I. cornuta*	leaves	Liao et al, 2013
89	Gouguside 5	*I. cornuta*	leaves	Liao et al, 2013
90	Gouguside 6	*I. cornuta*	leaves	Liao et al, 2013
91	Gouguside 7	*I. cornuta*	leaves	Liao et al, 2013
92	Ilexin L1	*I. pubescens*	roots	Staudt and Bertin, 1998
93	Ilexin L2	*I. pubescens*	roots	Staudt and Bertin, 1998
94	Ilexin L3	*I. pubescens*	roots	Staudt and Bertin, 1998
95	Ilexin L4	*I. pubescens*	roots	Staudt and Bertin, 1998
96	Ilexin L5	*I. pubescens*	roots	Staudt and Bertin, 1998
97	Ilexin L6	*I. pubescens*	roots	Staudt and Bertin, 1998
98	Ilexhainanoside A	*I. hainanensis*	leaves	Zhou et al, 2007
99	Ilexhainanoside B	*I. hainanensis*	leaves	Zhou et al, 2007
100	Acetylursolic acid	*I. paraguariensis*	leaves	De Souza et al, 2011
		I. kwantungensis	leaves	Kothiyal et al, 2012
101	Lucyoside H	*I. pubescens*	roots	Zhang et al, 2010
102	α-amyrin palmitate	*I. cornuta*	leaves	Wu et al, 2007
103	Ursolic acid	*I. asprella*	roots	Kothiyal et al, 2012
		I. cornuta	roots and leaves	Kothiyal et al, 2012
		I. latifolia	leaves	Kothiyal et al, 2012
		I. chinese	leaves	Kothiyal et al, 2012
		I. hainanensis	leaves	Kothiyal et al, 2012
104	Uvaol	*I. cornuta*	leaves	Kothiyal et al, 2012
		I. latifolia	leaves	Kothiyal et al, 2012
105	Mussaendoside R	*I. pubescens*	roots	Zhang et al, 2010
106	Monepaloside F	*I. asprella*	roots	Kothiyal et al, 2012
107	Oblonganoside B	*I. asprella*	roots	Kothiyal et al, 2012
108	Pomolic acid-28-*O*-β-*D*-glucopyranoside	*I. cornuta*	leaves	Wu et al, 2007
109	Pomolic acid	*I. rotunda*	root barks	
110	Rotundic acid	*I. rotunda*	root barks	Wu et al, 2007
		I. chinensis	leaves	Wu et al, 2007
		I. pubescens	roots	Zhang et al, 2010
111	Rotungenic acid	*I. rotunda*	fruits	Wu et al, 2009
112	Ilexgenin A	*I. pubescens*	roots and stems	Zhang et al, 2010
		I. hainanensis	leaves	
113	Ilexolic acid A	*I. asprella*	roots	Wu et al, 2007
		I. pubescens	roots	Zhang et al, 2010
114	Brevicuspisaponin 1	*I. brevicuspis*	leaves	Kothiyal et al, 2012
115	Brevicuspisaponin 2	*I. brevicuspis*	leaves	Kothiyal et al, 2012
116	Buxifoliside 1	*I. buxifolia*	leaves	Kothiyal et al, 2012
117	Affinoside 1	*I. affinis.*	leaves	Kothiyal et al, 2012
118	2,3,19-Trihydroxy-urs-12-ene-23,28-dioic acid	*I. asprella*	roots	Wang et al, 2013
119	3β-*O*-acetyluvaol	*I. asprella*	roots	Wang et al, 2013
120	3-*O*-α-*L*-arabinopyranosyl pomoli acid-28-*O*-6'-*O*-methyl-β-*D*-glucopyranoside	*I. cornuta*	leaves	Wang et al, 2013
121	2α,3β,19α,23-Tetrahydroxy-ursolicacid-12-en-28-oic acid	*I. chinensis*	leaves	Wang et al, 2013
122	2α,3β,19α,23-Tetrahydroxy-ursolicacid-12-en-28-oic-28-β-*D*-glucopyranoside	*I. chinensis*	leaves	Wang et al, 2013
123	3β-*O*-β-*D*-glucopyranosyl-(1→2)-α-*L*-2-*O*-arabinopyranosyl-19-hydroxyurs-12-en-28-oic acid 28-*O*-β-*D*-galactopyranosylurs ester	*I. amara*	leaves	Wang et al, 2013

To be continued

Continued Table 2

	Compounds	Botanical resources	Parts of plants	References
124	3β-*O*-β-*D*-glucopyranosyl-(1→2)-β-*D*-galactopyranosyl-urs-12-en-28-oic acid	*I. cornuta*	leaves	Wang et al, 2013
125	3β-*O*-β-*D*-glucopyranosyl-(1→2)-α-*L*-arabinopyranosyl-19-hydroxyurs-12-en-28-oic acid	*I. amara*	leaves	Wang et al, 2013
126	23-Methy lester of 20(*S*)-3β,19α,24-trihydroxyurs-12-en-23,28-dioic acid	*I. affinis*	leaves	Wang et al, 2013
127	(20*S*)-niga-ichigoside F1	*I. litseaefolia*	leaves	Wang et al, 2013
128	23-Hydroxy-ursolicacid-3-*O*-α-*L*-arabino-pyranosyl-(1→2)-β-*D*-glucuronopyranosyl-28-O-β-*D*-glucopyranoside	*I. cornuta*	leaves	Wang et al, 2013
129	3β-*O*-β-*D*-glucopyranosyl-(1→2)-α-*L*-arabinopyranosylurs-12-en-28-oic acid	*I. amara*	leaves	Wang et al, 2013
130	3β-*O*-β-*D*-glucopyranosyl-(1→3)-α-*L*-2-*O*-acetylarabinopyranosylurs-12-en-28-oicacid-28-*O*-β-*D*-glucopyranosyl ester	*I. amara*	leaves	Wang et al, 2013
131	3β-*O*-acetylursolil acid	*I. amara*	leaves	Wang et al, 2013
132	3β-*O*-β-*D*-glucopyranosyl-(1→3)-α-*L*-arabinopyranosyl-oleanolic acid	*I. buxifolia*	leaves	Wang et al, 2013
133	3β-Acetoxy ursolic acid	*I. cornuta*	roots	Wang et al, 2013
134	19α-Hydroxy ursolic acid	*I. cornuta*	roots	Wang et al, 2013
135	6'-*O*-acetyl-ilexsaponin A1	*I. pubescens*	roots	Kothiyal et al, 2012
136	12-Ursene-3,28-diol	*I. cornuta*	leaves	Kothiyal et al, 2012
137	19-Dehydroursolic acid	*I. asprella*	roots	Kothiyal et al, 2012
138	23-Hydroxyl-methyl ursolate	*I. cornuta*	roots	Kothiyal et al, 2012
139	23-Hydroxytormentic acid 28-*O*-β-*D*-glucopyranoside	*I. chinensis*	leaves	Kothiyal et al, 2012
140	23-Hydroxytormentic acid	*I. chinensis*	leaves	Kothiyal et al, 2012
141	28-*O*-β-*D*-glucopyranosyl pomolic acid	*I. asprella*	roots	Kothiyal et al, 2012
142	3-*O*-α-*L*-arabinopyranosyl pomoli acid-28-*O*-6'-*O*-methyl-β-*D*-glucopyranoside	*I. cornuta.*	leaves	Kothiyal et al, 2012
143	3-*O*-β-*D*-xylopyranosyl-3β-hydroxyurs-12, 18(19)-dien-28-oic acid 28-β-*D*-glucopyranosy lester	*I. asprella*	roots	Kothiyal et al, 2012
144	3β-Acetoxy-28-hydroxyurs-12-ene	*I. cornuta*	roots	Kothiyal et al, 2012
145	Ilexolide A	*I. crenata*	roots	Han et al, 1993
146	Ilexoside A	*I. chinensis*	leaves	Han et al, 1993
147	Ilexoside B methyl ester	*I. crenata*	leaves	Kakuno et al, 1991
148	Ilexoside II	*I. cornuta*	leaves	Han et al, 1993
149	Ilexoside III	*I. crenata*	fruits	Kakuno et al, 1991
150	Ilexoside IV	*I. crenata*	fruits	Kakuno et al, 1991
151	Ilexoside V	*I. crenata*	fruits	Kakuno et al, 1991
152	Ilexoside VI	*I. crenata*	fruits	Kakuno et al, 1991
153	Ilexoside VII	*I. crenata*	fruits	Kakuno et al, 1991
154	Ilexoside VIII	*I. crenata*	fruits	Kakuno et al, 1991
155	Ilexoside IX	*I. crenata*	fruits	Kakuno et al, 1991
156	Ilexoside X	*I. crenata*	fruits	Kakuno et al, 1991
157	Ilexoside XI	*I. crenata*	fruits	Kakuno et al, 1991
158	Ilexoside XII	*I. crenata*	fruits	Kakuno et al, 1991
159	Ilexoside XIII	*I. crenata*	fruits	Kakuno et al, 1991
160	Ilexoside XIV	*I. crenata*	leaves	Kakuno et al, 1991
161	Ilexoside XLI	*I. rotunda*	leaves	Amimoto et al, 1993b
162	Ilexoside XLII	*I. rotunda*	leaves	Amimoto et al, 1993b
163	Ilexoside XLIII	*I. rotunda*	leaves	Amimoto et al, 1993b

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Continued Table 2

	Compounds	Botanical resources	Parts of plants	References
164	Ilexoside XLIV	*I. rotunda*	leaves	Amimoto et al, 1993b
165	Ilexoside XLV	*I. rotunda*	leaves	Amimoto et al, 1993b
166	Ilexoside XLX	*I. crenata*	root barks	Kakuno et al, 1991
167	Ilexoside XXI	*I. crenata*	root barks	Kakuno et al, 1991
168	Ilexoside XXII	*I. crenata*	root barks	Kakuno et al, 1991
169	Ilexoside XXIII	*I. crenata*	root barks	Kakuno et al, 1991
170	Ilexoside XXIV	*I. crenata*	root barks	Kakuno et al, 1991
171	Ilexoside XXV	*I. crenata*	root barks	Kakuno et al, 1991
172	Ilexoside XXVII	*I. integra*	leaves	Han et al, 1993
173	Ilexoside XXVIII	*I. integra*	leaves	Han et al, 1993
174	Ilexoside XXX	*I. rotunda*	leaves	Amimoto et al, 1993b
175	Ilexoside XXXI	*I. rotunda*	leaves	Amimoto et al, 1993b
176	Ilexoside XXXIV	*I. rotunda*	leaves	Amimoto et al, 1993b
177	Ilexoside XXXIX	*I. rotunda*	leaves	Amimoto et al, 1993b
178	Ilexoside XXXV	*I. rotunda*	leaves	Amimoto et al, 1993b
179	Ilexoside XXXVI	*I. rotunda*	leaves	Amimoto et al, 1993b
180	Ilexoside XXXVII	*I. rotunda*	leaves	Amimoto et al, 1993b
181	Ilexoside XXXVIII	*I. rotunda*	leaves	Amimoto et al, 1993b
Sterols				
182	β-Daucosterol	*I. rotunda*	root barks	Amimoto et al, 1993a; Zhu et al, 2008
		I. cornuta	roots	Han et al, 1987
		I. pubescens	roots and stems	
183	β-Sitosterol	*I. centrochinensis*	leaves	Lin et al, 1994
		I. rotunda	root barks	Amimoto et al, 1993a; Bai et al, 2011
		I. asprella	roots	Zhu et al, 2008
		I. cornuta	roots and leaves	Han et al, 1987
		I. pubescens	roots	
184	Spinasterol	*I. pubescens*	roots	Han et al, 1987
185	Stigmasterol	*I. pubescens*	roots	Han et al, 1987
Flavonids				
186	Hesperetin	*I. centrochinensis*	leaves	Lin et al, 1994
187	Hesperidin	*I. centrochinensis*	leaves	Lin et al, 1994
188	Astragalin	*I. centrochinensis*	leaves	Lin et al, 1994
189	Naringenin	*I. centrochinensis*	leaves	Lin et al, 1994
190	Poncirin	*I. centrochinensis*	leaves	Lin et al, 1994
191	Rhoifolin	*I. centrochinensis*	leaves	Lin et al, 1994
192	Apigenin	*I. centrochinensis*	leaves	Lin et al, 1994
193	Huazhongilexone	*I. centrochinensis*	leaves	Lin et al, 1994
197	Kaempferol-3-*O*-β-*D*-glucopyranoside	*I. cornuta*	leaves	Zhu et al, 2008
198	Rutin	*I. asprella*	leaves	Bai et al, 2011
199	Kaempferol	*I. cornuta*	leaves	Li et al, 2009
		I.pernyi	leaves	Hao et al, 2013
200	Kaempferol-3-*O*-sambubioside	*I. centrochinensis*	leaves	Li et al, 2011
Lignans				
204	(+)-Cycloolivil 6-*O*-β-*D*-glucopyranoside	*I. pubescens*	roots	Wang et al, 2008b
206	(+)-Cycloolivil	*I. pubescens*	roots	Wu et al, 2009
	(*2R,3S,4S*)-4-(4-hydroxy-3-methoxybenzyl)-2-(5-hydroxy-3-methoxyphenyl)-3-hydroxymethyl-tetrahydrofuran-3-ol	*I. cornuta*	leaves	Qin et al, 1986
224	Huazhongilexin	*I. centrochinensis*	leaves	Li et al, 2011
226	Liriodendrin	*I. pubescens*	roots	Han et al, 1993
227	Disyringin ether	*I. rotunda*	root barks	Wen and Chen, 1996

To be continued

Continued Table 2

	Compounds	Botanical resources	Parts of plants	References
230	(+)-Syringaresino-1-*O*-β-*D*-glucopyranoside	*I. pernyi*	leaves	Xie et al, 2007
231	(+)-Pinoresinol-4,4'-*O*-bisglucopyranoside	*I. pubescens*	roots	Wu et al, 2009
232	(+)-Fraxiresinol-1-*O*-β-*D*-glucoside	*I. pubescens*	roots	Wu et al, 2009
233	Magnolenin C	*I. pubescens*	roots	Wu et al, 2009
234	Sinapicaldehyde4-*O*-β-*D*-glucopyranoside	*I. pubescens*	roots	Wu et al, 2009
235	Syringaresinolmono-β-*D*-glucoside	*I. pubescens*	roots	Wu et al, 2009
236	Tortoside A	*I. pubescens*	roots	Wu et al, 2009
Phenolic acids and fatty acids				
202	P-hydroxy pheny lethanol	*I. pubescens*	roots	Wang et al, 2008b
203	β-*D*-mudanoside A	*I. pubescens*	roots	Wang et al, 2008b
205	4,5-di-*O*-caffeoylquinic acid	*I. pubescens*	roots	Wang et al, 2008b
207	Hydroquinone	*I. pubescens*	roots	Wu et al, 2009
208	Protocatechuic aldehyde	*I. pubescens*	roots	Wu et al, 2009
209	Dihydroxyacetophenone	*I. pubescens*	roots	Wu et al, 2009
210	Methyl-2,4-dihydroxybenzoate	*I. cornuta*	leaves	Qin et al, 1986
212	Caffeic acid 4-*O*-β-*D*-glucopyranoside	*I. rotunda*	root barks	Sun et al, 2009
213	Coniferylaldehyde	*I. asprella*	roots	Wang et al, 2009
214	2,4,6-Trihydroxytoluene	*I. centrochinensis*	leaves	Li et al, 2011
215	Stearic acid	*I. rotunda*	root barks	Sun et al, 2009
216	Vanillic acid 4-*O*-β-*D*-glucopyranoside	*I. rotunda*	root barks	Sun et al, 2009
217	Nonadecylic acid	*I. rotunda*	root barks	Sun et al, 2009
218	N-behenic acid	*I. cornuta*	leaves	Wu et al, 2008
219	Heptanoic acid	*I. cornuta*	roots	Wu et al, 2008
220	Protocatechuic acid	*I. asprella*	roots	He et al, 2012
221	Triacontanoic acid	*I. asprella*	leaves	He et al, 2012
222	Cafeic acid	*I. asprella*	roots	He et al, 2012
		I. pubescens	roots	
223	Homovanillic acid	*I. pubescens*	roots	Wu et al, 2009
225	Acteoside	*I. pubescens*	roots	Han et al, 1993
Others				
194	Aesculetin	*I. pubescens*	roots	Han et al, 1987
195	Scopoletin	*I. pubescens*	roots	Han et al, 1987
196	Umbelliferone	*I. pubescens*	roots	Han et al, 1987
201	Physcion	*I. cornuta*	leaves	Li et al, 2009
228	Sinapaldehydeglucoside	*I. rotunda*	root barks	Sun et al, 2009
229	Amarantholidoside IV	*I. pernyi*	leaves	Xie et al, 2007

2.1.1 Lupane pentacyclic triterpenoids

Fourteen lupane pentacyclic triterpenoids were isolated from eight species (Table 2 and Figure 2). *I. crenata* (**3** and **5−8**) is the most species intensively studied followed by *I. cornuta* (**9** and **11−13**). Compounds **3** and **5−8** were only isolated from the fruits.

2.1.2 Oleanane pentacyclic triterpenoids

A total of 41 oleanane pentacyclic triterpenoids have been isolated from the leaves, roots, and root barks of 11 species in *Ilex* L. (Table 2 and Figure 3). *I. rotunda* is the most species that contains plenty of oleanane pentacyclic triterpenoids (**29−36**, **42**, **43**, and **48**). *I. cornuta* and *I. asprella* are the second one including six compounds, respectively, **19**, **20**, **22**, **28**, **49**, and **50** from *I. cornuta* and **15−17**, **21**, **27**, and **45** from *I. asprella*. Five oleanane pentacyclic triterpenoids have been isolated from *I. crenata* (**37−41**) and four from *I. latifolia* (**23−25** and **51**). Other compounds are shown in Table 2. All of them are absent from the fruits.

2.1.3 Ursane pentacyclic triterpenoids

There are 126 ursane pentacyclic triterpenoids in 17 species of *Ilex* L. that is much more than other chemical classes (Table 2 and Figure 4). Twenty-five compounds (**56−59**, **85−91**, **102−104**, **108**, **120**, **124**, **133**, **136**, **138**, **142**, **144**, and **148**) have been isolated from *I. cornuta*, 20 compounds (**145**, **147**, **149−160**, and **166−171**) from *I. crenata*, 17 compounds (**69**, **109−111**, **161−165**, and **174−181**) from *I. rotunda*, 17 compounds (**64−68**, **92−97**, **101**, **105**, **110**, **112**, **113**, and **135**) from *I. pubscens*, nine compounds (**70−74** and **77−80**) from *I. kudingcha*, eight compounds (**76**, **81−84**, **103**, and **104**) from *I. latifolia*, eight

compounds (**103**, **106**, **107**, **113**, **118**, **119**, **137**, **141**, and **143**) from *I. asprella*, and seven compounds (**103**, **110**, **121**, **122**, **139**, **140**, and **146**) from *I. chinensis*. Five compounds have been isolated from *I. paraguariensis* (**60−63** and **100**), *I. amara* (**123**, **125**, and **129−131**), and *I. hainanensis* (**64, 98, 99, 103**, and **112**), respectively.

2.2 Flavonoids

Twelve flavonoids were isolated from the leaves or roots of five in species *Ilex* L.: eight compounds (**186−193**) from the leaves of *I. centrochinensis*, two compounds (**198** and **199**) from the leaves of *I. asprella*, and compound **200** from the leaves of *I. pernyi.* Compound **193** is a flavonoid only isolated from genus *Ilex* L. (Table 2 and Figure 5).

2.3 Lignans

Thirteen phenols were isolated largely from five plants in *Ilex* L. species: three compounds (**204**, **206** and **209**) from the roots of *I. pubescens*. **224**, **226** and **227** have been isolated from three species of *Ilex L.*: *I. centrochinensis*, *I. pubescens*, and *I. rotunda*, in which huazhongilexin (**224**) was isolated only from this genus. **230** were isolated from the leaves of *I. pernyi*, and **231−236** were isolated from the roots of *I. pubescens* (Table 2 and Figure 6).

2.4 Phenolic acids and fatty acids

Twenty phenolic acids and fatty acids were isolated from four species of *Ilex* L.: **202**, **203**, **205** and **207−209** were from roots of *I. pubescens*, compound **210** from leaves of *I. cornuta*, compound **212** from root barks of *I. rotunda*, compound **213** from roots of *I. asprella*, and compound **214** from leaves of *I. centrochinensis.* Compounds **215−217** from the root barks of *I. rotunda*, **220−222** from the roots or leaves of *I. asprella*, **218** and **219** from the roots or leaves of *I. cornuta*, **223** and **225** from the roots of *I. pubescens* (Table 2 and Figure 7)

2.5 Sterols

Four sterols (**182−185**) were isolated from five species of *Ilex* L.: *I. centrochinensis*, *I. asprella*, *I. cornuta*, *I. pubescens*, and *I. hainanensis* (Table 2 and Figure 8).

2.6 Minerals

Up to now, contents of eight elements (Fe, Ca, Mn, Mg, Na, K, Zn, and Cu) in the leaves of *I. paraguariensis* were determined by atomic absorption spectrophotometer (Vera et al, 1997), so did in the leaves of *I. kudingcha* (Zn, Cu, Mg, Fe, Ca, Mg, Sr, Co, Li, Rb, K, and Ni). Zhang (2002) found that *I. kudingcha* was more than others in the contents of Zn, Mn, Cu, Mg, K, Rb, Fe, and Li.

2.7 Others

Three coumarin compounds (**194−196**) from the roots of *I. pubescens*. Compound **228** was isolated from *I. rotunda,* **229** and **230** were isolated from the leaves of *I. pernyi* (Table 2 and Figure 9).

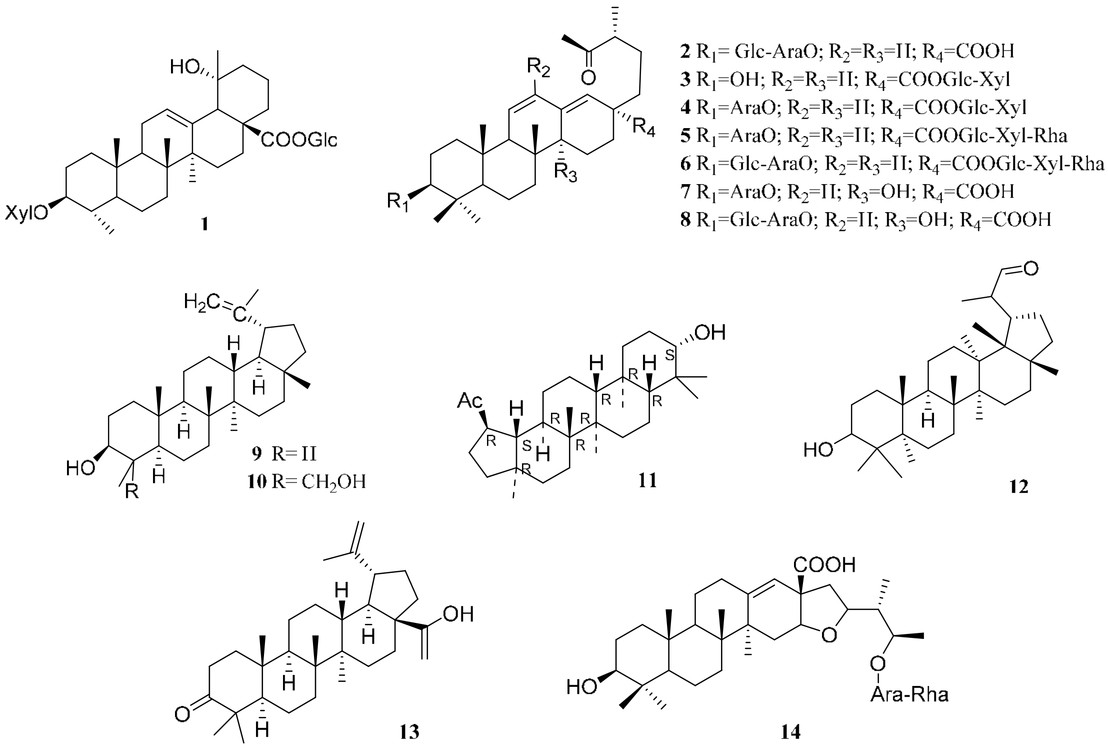
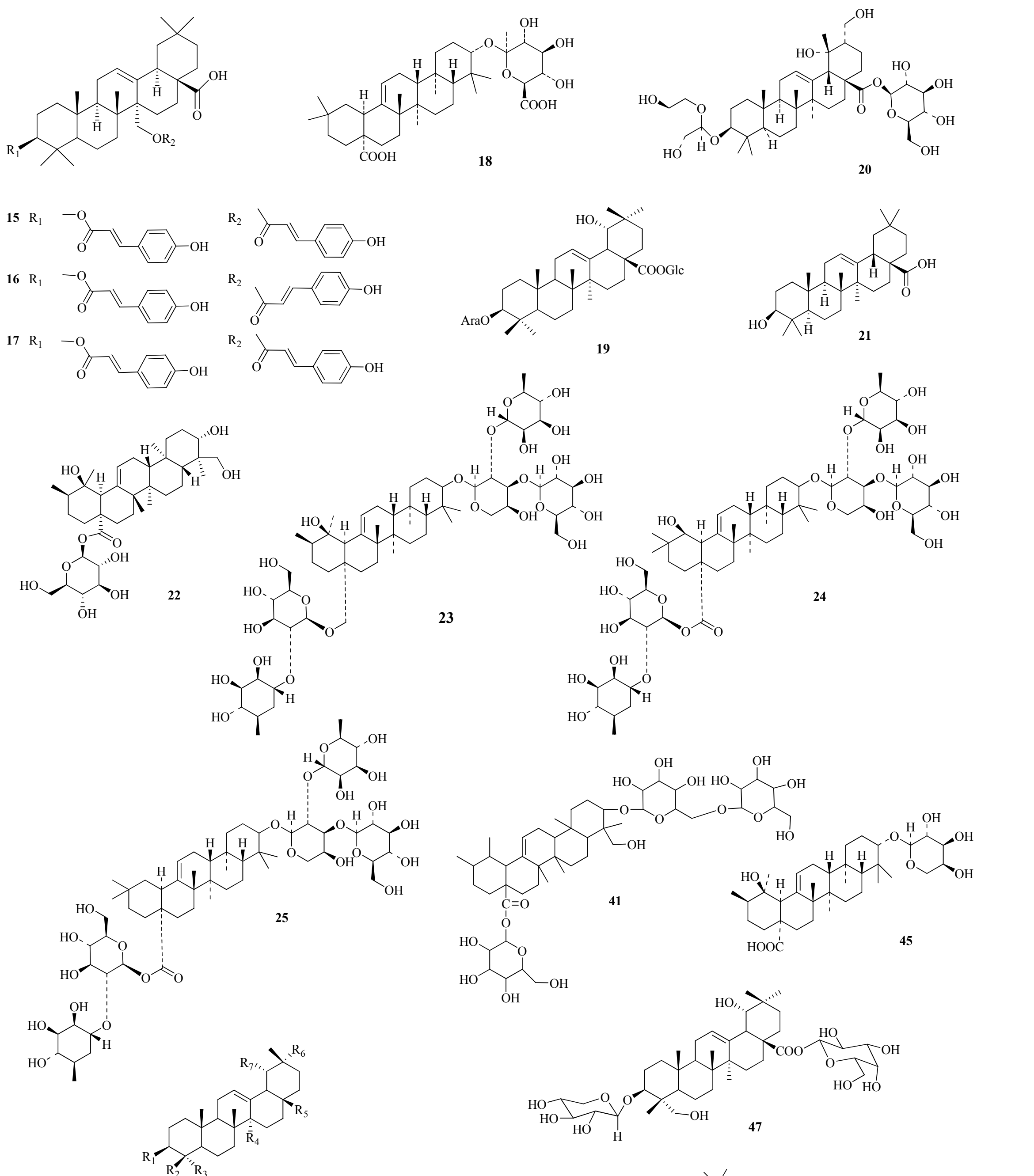


Figure 2 Chemical structures of lupane pentacyclic triterpenoids



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27 R_1= R_7=OH;R_2=R_3=R_4=R_6=H;R_5=COOH
28 R_1= OH;R_2=R_3=R_4=R_6=CH_3;R_5=COOH;R_7=H
29 R_1= R_7=OH;R_2=R_3=R_4=R_6=H;R_5=COOH
30 R_1= GlcO;R_2=CH_2OH;R_3=R_4=R_6=CH_3;R_5=COOGlc;R_7=H
31 R_1= Gal-GlcO;R_2=R_4=R_6=CH_3;R_3=$COOH_3$;R_5=COOH;R_7=OH
32 R_1= GlcO;R_2=CH_2OH;R_3=R_4=R_6=CH_3;R_5=COOGlc;R_7=H
33 R_1= Gal-GlcO;R_2=R_6=CH_3;R_3=CH_2OH;R_4=R_7=H;R_5=COOGlc
34 R_1= GlcO;R_2=CH_3;R_3=CH_2OH;R_4=CH_3;R_5=COOGlc;R_6=CH_3;R_7=OH
35 R_1= GlcO;R_2=CH_2OH;R_3=R_4=R_6=CH_3;R_5=COOGlc;R_7=OH
36 R_1= GlcO;R_2=R_4=R_6=CH_3;R_3=CH_2OH;R_5=COOGlc;R_7=H
37 R_1= Glc-AraO;R_2=CH_3=R_4=R_6=CH_3;R_5=COOGlc;R_7=OH
38 R_1= Glc-Ara-AcO;R_2=R_3=R_4=R_6=CH_3;R_5=COOGlc;R_7=OH
39 R_1= Glc-Glc-AraO;R_2=R_3=R_4=R_6=CH_3;R_5=COOGlc;R_7=OH
40 R_1= Glc-AraO;R_2=R_3=R_4=R_6=CH_3;R_5=COOGlc-Rha-Xyl;R_7=OH
42 R_1= GlcO;R_2=R_4=R_6=CH_3;R_3=CH_2OH;R_5=COOH;R_7=OH
43 R_1= GlcO;R_2=R_4=R_6=CH_3;R_3=CHO;R_5=COOH;R_7=OH
44 R_1= $COCH_3$;R_2=R_4=R_7=H;R_3=R_6=CH_3;R_5=COOH
46 R_1= Glc(1®2)(CH_3OOC)GlcO;R_2=R_3=R_4=R_6=R_7=H;R_5=COOGlc
52 R_1= Glc-Glc(CH_3OOC)O;R_2=R_3=R_4=R_6=CH_3;R_5=COOGlc;R_7=H
53 R_1= Rha-Ara-GlcO;R_2=R_3=R_4=R_6=CH_3;R_5=COOH;CH_3;R_7=H
54 R_1= Glc-Ara(AcO)O;R_2=R_3=R_4=R_6=CH_3;R_5=COOGlc;R_7=H
55 R_1=R_7= OH;R_2=R_4=R_6=H;R_3=R_5=COOH

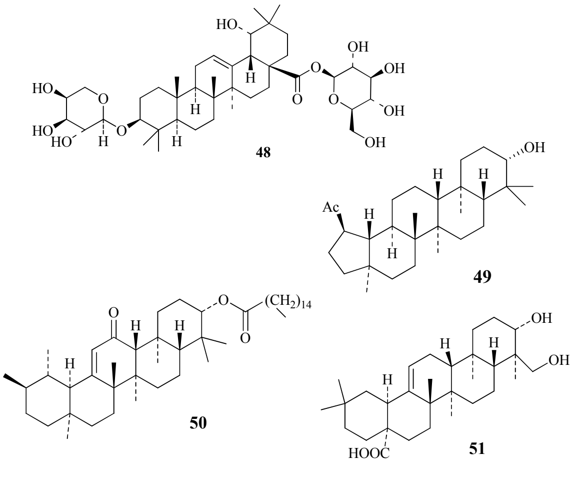
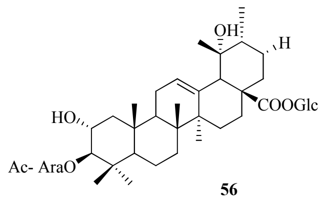


Figure 3 Chemical structures of oleanane pentacyclic triterpenoids



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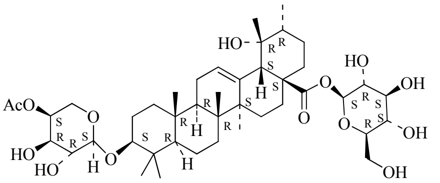

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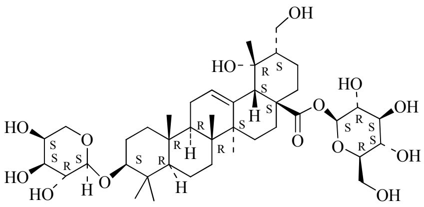

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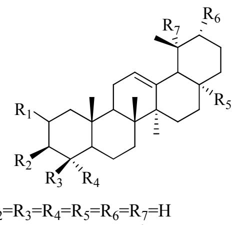
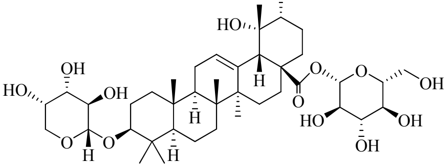


59 R_1=R_2=R_3=R_4=R_5=R_6=R_7=H
60 R_1=R_3=R_7=H; R_2=Ara-GlcO; R_4=R_6=CH_3;R_5=COOGlc
61 R_1=R_3=R_7=H; R_2=Glc-Glc-RhaO; R_4=R_6=CH_3;R_5=COOGlc
62 R_1=R_3=R_7=H; R_2=Glc-GlcO; R_4=R_6=CH_3;R_5=COOGlc-Glc
63 R_1=R_3=R_7=H; R_2=Glc-Glc-RhaO;R_4=R_6=CH_3;R_5=COOGlc-Glc
64 R_1=R_2=R_7=OH;R_3=R_6=CH_3; R_4=COOH;R_5=COOGlc
65 R_1=R_3=R_4=R_6=R_7=H; R_2=XylO;R_5=COOGlc
66 R_1=R_7=OH; R_2=Glc-XylO;R_3=R_4=R_6=CH_3;R_5=COOH
67 R_1=R_7=OH; R_2=Rha-Glc-XylO;R_3= R_4=R_6=CH_3;R_5=COOH
68 R_1=R_7=OH; R_2=Glc-XylO;R_3=R_4=R_6=CH_3;R_5=COOGlc



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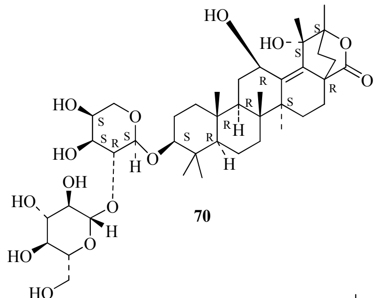

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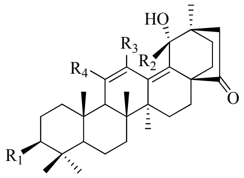
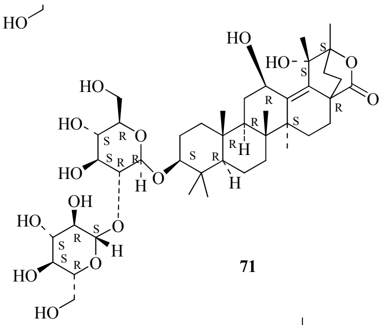


72 R_1=Rha-GlcO; R_2=CH_3;R_3=R_4=H;
73 R_1=Glc-AraO; R_2=CH_3;R_3=OH; R_4=H;
74 R_1=Rha-AraO; R_2=CH_3;R_3=H; R_4=OH;
75 R_1=Glc-GlcO; R_2=R_3=H; R_4=OH;
76 R_1=Glc-AraO; R_2=CH_3;R_3=R_4=H;
77 R_1=Glc-AraO; R_2=CH_3;R_3=OH=OH;
78 R_1=Rha-GlcO; R_2=CH_3;R_3=OH; R_4=H;
79 R_1=Rha-AraO; R_2=CH_3;R_3=R_4=OH;
80 R_1=Rha-GlcO; R_2=CH_3;R_3=H; R_4=OH;



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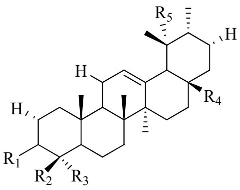
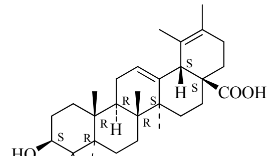


81 R_1=Rha-GlcO;R_2=R_5=H;R_3=CH_3;R_4=CH_2OH
82 R_1=Rha-GlcO; R_2=R_5=H;R_3=CH_3,R_4=COOH
83 R_1=Rha-Ara-GlcO; R_2=R_5=H;R_3=CH_3;R_4=COOGlc
84 R_1=Glc-Glc-Ara-RhaO; R_2=H;R_3=CH_3,R_4=C_{28}OOH; R_5=OH
85 R_1=AraO;R_2=H;R_3=CH_3,R_4=C_{28}OOH; R_5=OH
86 R_1=GlcO; R_2=H;R_3=CH_3,R_4=C_{28}OOGlc; R_5=OH
87 R_1=Glc-GlcO; R_2=R_5=H;R_3=CH_3,R_4=C_{28}OOGlc
88 R_1=Glc-GlcO; R_2=H;R_3=CH_3,R_4=C_{28}OOGlc; R_5=OH
89 R_1=Ara-GlcO; R_2=H;R_3=CH_3,R_4=C_{28}OOGlc; R_5=OH
90 R_1=Ac-Ara-GlcO; R_2=H;R_3=CH_3,R_4=C_{28}OOGlc; R_5=OH
91 R_1=AraO;R_2=H;R_3=CH_3,R_4=C_{28}OOGlc; R_5=OH
92 R_1= R_4=R_5=OH; R_2=COOH;R_3=H
93 R_1=R_5=OH; R_2=COOH;R_3=H; R_4=OGlc
94 R_1=Glc-Xyl-XylO; R_2=R_3=H; R_4=R_5=OH
95 R_1=Rha-Glc-Xyl-XylO; R_2=R_3=H; R_4=COOH;R_5=OH
96 R_1=Glc-Xyl-XylO; R_2=R_3=H; R_4=COOGlc;R_5=OH
97 R_1=XylO; R_2=R_5=OH;R_3=H; R_4=COOGlc
98 R_1=OH; R_2=R_5=H;R_3=COOH; R_4=COOGlc
99 R_1=OH; R_2=H;R_3=COOH; R_4=COOGlc;R_5=CH_2OH
100 R_1=OH; R_2=R_5=H;R_3=CH_3; R_4=COOH
101 R_1=GlcO; R_2=R_3=R_5=H; R_4=COOGlc
102 R_1=C_{15}COO; R_2=R_3=R_4=R_5=H
103 R_1=OH; R_2=R_5=H;R_3=CH_3; R_4=COOH
104 R_1=OH; R_2=R_5=H;R_3=CH_3; R_4=CH_2OH
105 R_1=GlcO; R_2=R_3=H; R_4=COOGlc;R_5=OH



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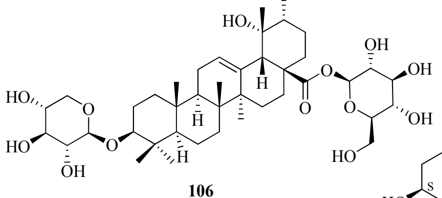

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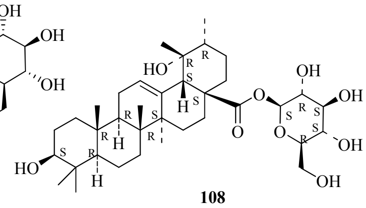

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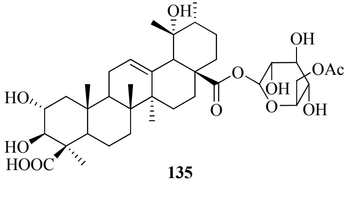

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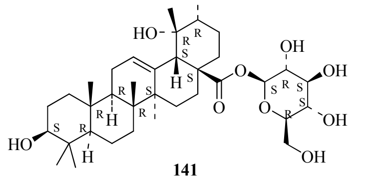

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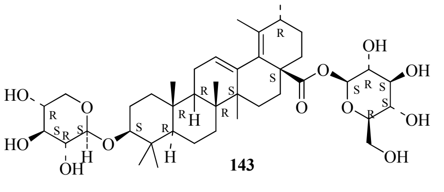

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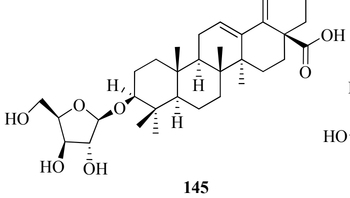

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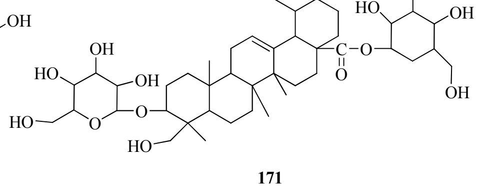

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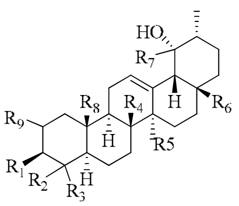

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111 R_1=R_9=OH;R_2=R_6=COOH;R_3=CH_3;R_4=R_5=R_7=R_8=H
112 R_1=R_9=OH;R_2=R_6=COOH;R_3=CH_3;R_4=R_5=R_7=R_8=H
113 R_1=R_9=OH;R_2=CH_3;R_3=CH_2OH;R_4=R_5=R_7=R_8=H;R_6=COOH
114 R_1=AraO;R_2=CH_2OH;R_3=CH_3;R_4=R_5=R_7=R_8=H;R_6=$C_{28}OOH$;R_9=OH
115 R_1=AraO;R_2=R_3=CH_2OH;R_4=R_5=R_7=R_8=R_9=H;R_6=$C_{28}COOH$
116 R_1=R_9=OH;R_2=CH_3;R_3=COOH;R_4=R_5=R_7=R_8=H;R_6=COOGlc
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125 R_1=Glc(1®2)-AraO;R_2=R_3=CH_3;R_4=R_5=R_7=R_8=R_9=H;R_6=$C_{28}OOGlc$
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159 R_1=Glc-Glc-AraO;R_2=R_3=CH_3;R_4=R_5=R_7=R_8=R_9=H;R_6=COOGlc-Rha-Xyl
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174 R_1=R_9=OH;R_2=R_3=CH_3;R_4=R_5=R_7=R_8=H;R_6=COOGlc
175 R_1=GlcO;R_2=R_3=R_5=CH_3;R_4=R_7=R_8=R_9=H;R_5=CH_3;R_6=COOGlc
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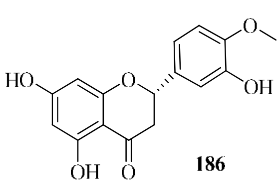
177 R_1=GlcO;R_2=CH_3,R_3=CH_2OH;R_4=R_5=R_7=R_8=H;R_6=COOGlc;R_9=OH
178 R_1=OSO_3Na;R_2=CH_2OH,R_3=CH_3;R_4=R_5=R_7=R_8=H;R_6=COOGlc;R_9=OH
179 R_1=GlcO;R_2=CH_2OH,R_3=CH_3;R_4=R_5=R_7=R_8=H;R_6=COOGlc;R_9=OH
180 R_1=GlcO;R_2=CH_3,R_3=CH_2OH;R_4=R_5=R_7=R_8=H;R_6=COOGlc;R_9=OH
181 R_1=R_9=OH;R_2=CH_3,R_3=CH_2OGlc;R_4=R_5=R_7=R_8=H;R_6=COOGlc

Figure 4 Chemical structures of ursane pentacyclic triterpenoids



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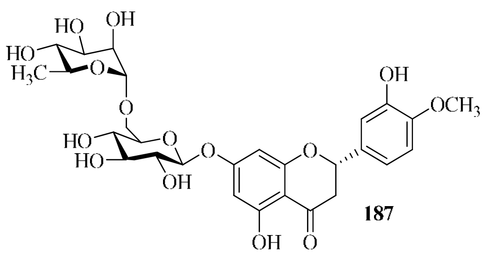

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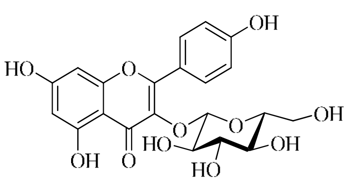

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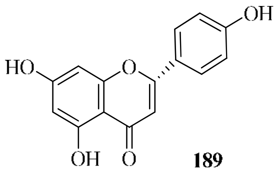

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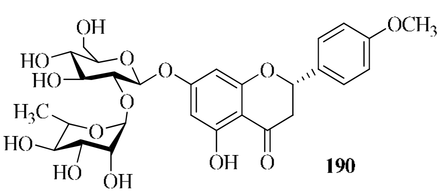

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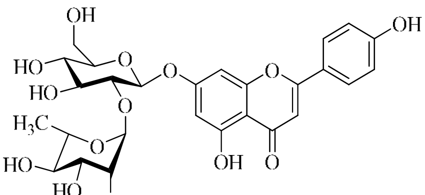

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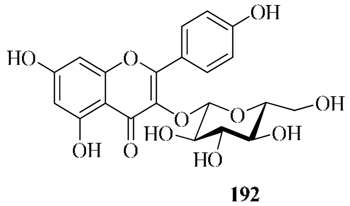

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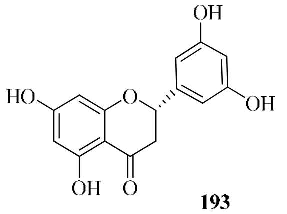

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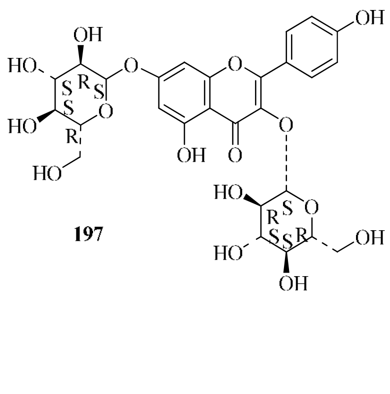

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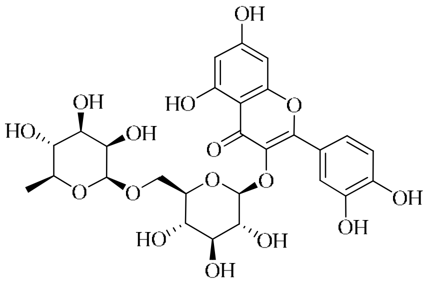

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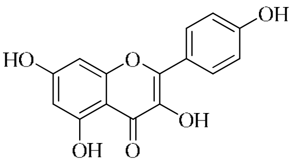

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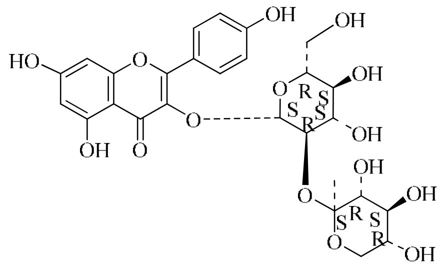

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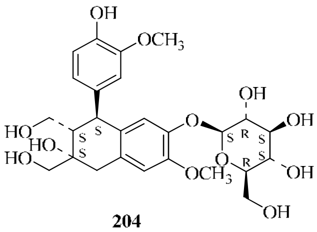
Figure 5 Chemical structures of flavonoids



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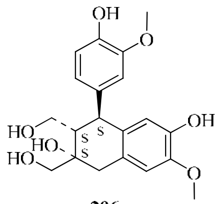

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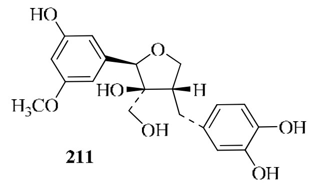

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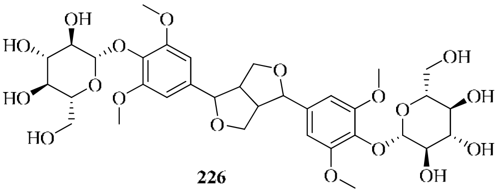

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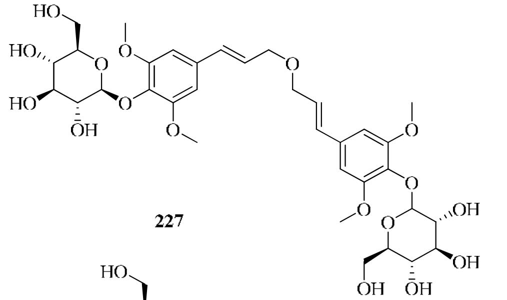

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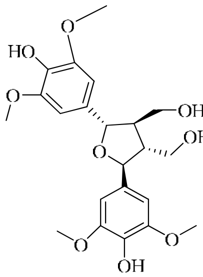

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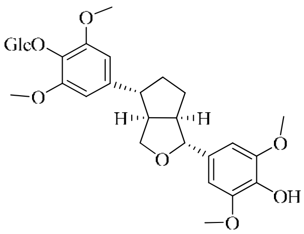

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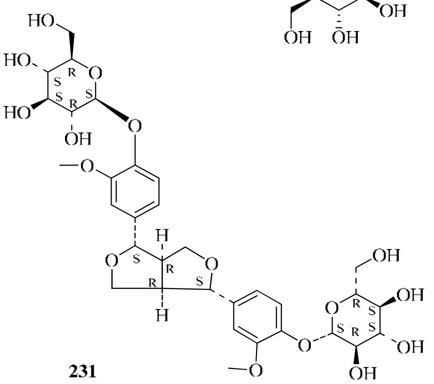

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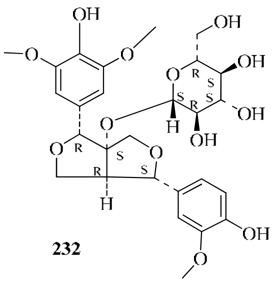

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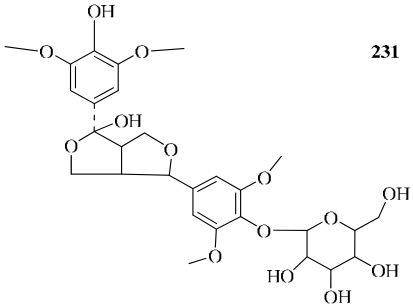

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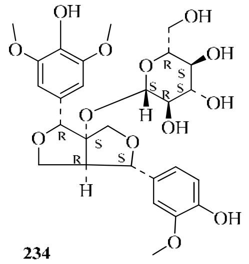

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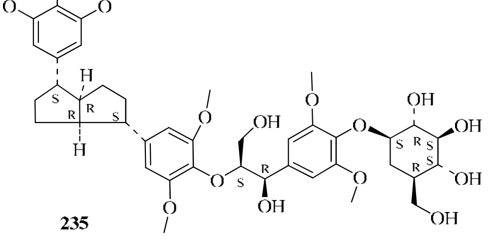

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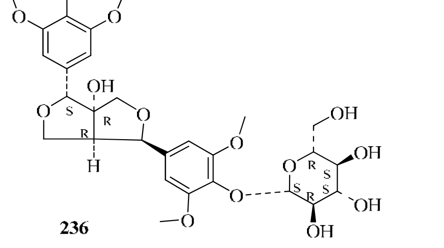

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Figure 6 Chemical structures of lignans

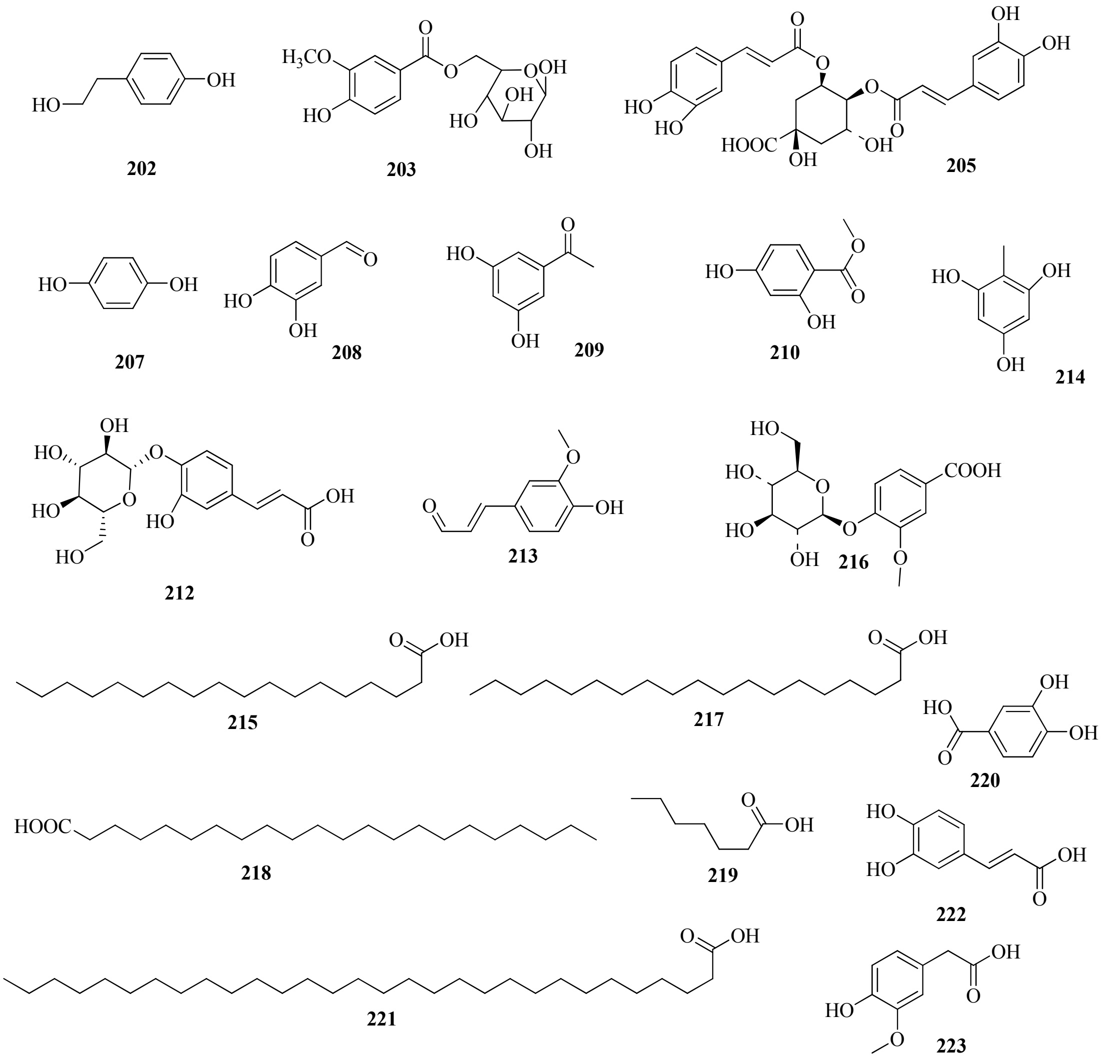

Figure 7 Chemical structures of phenolic acids and fatty acids

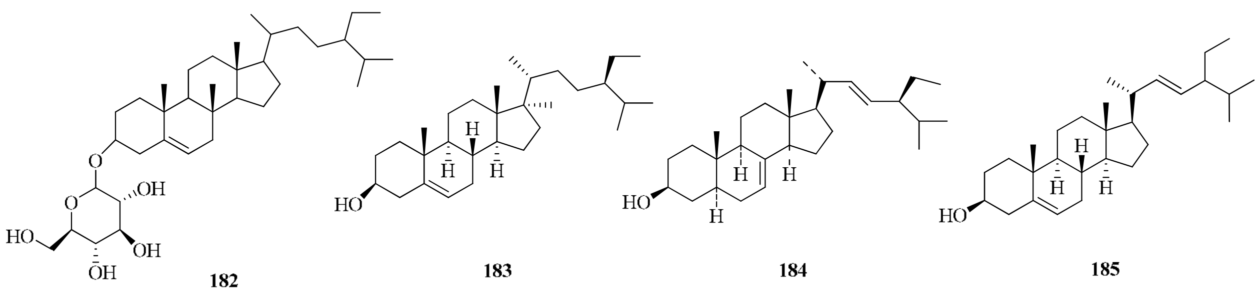

Figure 8 Chemical structures of sterols

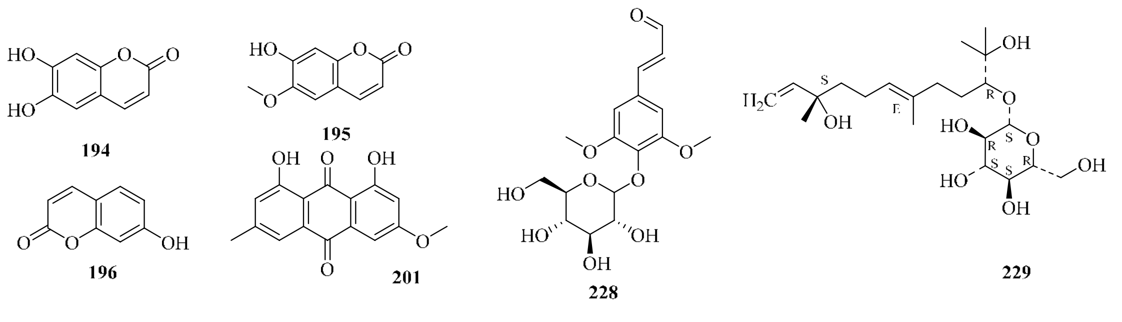

Figure 9 Chemical structures of others

3. Ethnopharmacology of plants in *Ilex* L.

The *Ilex* L. species were first described in *Compendium of Materia Medica* (Ming dynasty), in which *I. chinensis* and *I. cornuta* are recorded in morphology and efficiency. The leaves of *I. chinensis* can dispel the pathogenic wind from muscles, and those of *I. cornuta* are used to treat leukodermia after boiled (Li, 2003).

Generally, the medicinal plants from the genus *Ilex L.* are cool or cold in nature and bit in taste. *Ilicis Chinensis Folium* (dried leaves of *I. chinensis*), *Ilicis Cornutae Folium* (dried leaves of *I. cornuta*), and *Ilicis Rotundae Cortex* (dried root barks of *I. routunda*) have been widely used as traditional medicines in China and all recorded in the *Chinese Pharmacopoeia 2015* (Pharmacopoeia Committee of P R. China, 2015). *Ilicis Chinensis Folium*, bitter and cool, enters the meridians in the lung, intestine, and urinary bladders, with the functions in cooling heat and dispelling blood stasis. *Ilicis Cornutae Folium*, bitter and cool, enters the meridians in the lung and kidney, with the functions in cooling heat and nourishing the kidney *Yin*. *Ilicis Rotundae Cortex*, bitter and cold, enters the meridians in the lung, intestine, liver, and stomach, with the functions in cooling heat and relieving pain.

The leaves of *I. kudingcha*, and *I. latifolia* are benefit to human health such as to treat sore throat, diuretic, headache and weight loss. The fruits, roots, and leaves of *I. cornuta* have a broad spectrum of bioactivities of anti-inflammation, anti-microbe, and anti-hypertension. In China, *I. rotunda* is used as a remedy for scalds, burns, bleeding control and binding medicine. *I. chinensis* has been used in the treatment of bacterial diseases, tonsillitis, urinary tract infections, and common cold. The roots of *I. pubescens* were used to treat cardiovascular diseases and hypercholestaemia (Table 3).

The leaves of Kudingcha (*I. latifolia* and *I. kudingcha*), Yerba Mate (*I. paraguariensis* and *I. brevicuspis*), yaupon (*I. vomitoria*), Appalachian tea (*I. glabra*), guayusa tea (*I. guayusa*), etc, are used as teas in some cultures. They are called non-*Camellia* teas−the term that describes such plants as absent from the genus *Camellia* L. (Theaceae) are non- alcoholic beverages. Modern pharmacological studies elucidated that non-*Camellia* teas can potentially prevent chronic metabolic diseases by reducing hypoglycemia, hyperlipidemia, and

Table 3 Traditional uses of medicinal plants from *Ilex* L.

Species in *Ilex* L.	Used parts	Functions	Clinical application
I. aculeolata	root barks	Calming endogenous wind, and clearing heat-toxin	Treat cold cough, burns and toothache
I. asprella	roots and leaves	Clearing heat-toxin, promoting fluid production, and removing blood stasis	Treat cold, headache, lung abscess, sore throat, furunculosis, contusions and strains, and hemorrhoids blood
I. chinensis	leaves	Clearing heat-toxin, promoting blood circulation, promoting granulation, and astringing sores	Treat lung heat cough, sore throat, diarrhea, abdominal diarrhea, coronary heart disease, angina, burns, leg ulcer, frostbite, furunculosis, urinary tract infection, and leprelcesis
I. cornuta	leaves, roots and root barks	Clearing heart-fire, dispersing the stagnated liver, benefiting the liver, eliminating dampness, and dispelling pathogenic wind	Treat cough, hemoptysis, dizziness, rheumatism, vitiligo, joint pain, toothache, and urticaria
I. dasygphylla	roots	Clearing heat-toxin	Unknown swelling
I. ficoidea	roots	Clearing heat-toxin, detumescence, and relieving pain	Treat hepatitis, and traumatic injury
*I. kwangtungen*sis	roots and leaves	Clearing heat-toxin, detumescence, and relieving pain	Treat hepatitis, traumatic injury, swelling, and joint pain
I. latifolia	leaves	Clearing heat-toxin, promoting fluid production, and slake thirst	The raw material of large-leaved tea; treat wind-heat headache, rhinitis, mouth inflammation, swelling and pain, thirst after the illness, and malaria
I. macroccarpa	roots	Clearing heat-toxic, astringing the lung, and relieving cough	Treat hyperactivity cough, hemoptysis, mist, and sore throat
I. micrococca	leaves and roots	Clearing heat-toxin, detumescence and relieving the pain	Treat traumatic injury, swelling, joint pain
I. pedunculosa	leaves	Hemostasis, removing blood stasis, and removing dampness	Treat rheumatic pain, bleeding, skin chapped, and abscess
I. pernyi	roots, fruits and leaves	Clearing heat-toxic, nourishing the liver, and invigorating kidney	Treat hyperactivity cough, hemoptysis, and sore throat
I. pubescens	roots	Clearing heat-toxic, promoting blood circulation, and removing obstruction in collaterals	Treat hyperactivity cough, sore throat, stroke, thrombosis obliterans, erysipelas, burns injury, ulcer, central retinitis, swelling and aching of gum

To be continued

Continued Table 3

Species of *Ilex* L.	Used parts	Functions	Clinical applications
I. rotunda	barks and root barks	Clearing heat and remove toxicity, promote dieresis, and alleviate pain.	Treat eczema, rheumatic arthritis, traumatic injury, sores and boils, sore throat, diarrhea due to damp-heat, abdominal distension, and fever due to sommer-heat and dampness
I. serrata	leaves and roots	Clearing heat-toxin, activating blood circulation, and cooling blood	Treat burns, trauma, bleeding, ulcers, and the lung abscess
I. suaveolens	roots	Eliminating slough, promoting granulation, resolving carbuncle, and relieving pain	Treat muscle strain
I .triflora	roots	Clearing heat-toxin	Treat furunculosis, contusions, and strains
I. viridis	leaves and roots	Cooling blood, detoxication, relieving pain, and eliminating slough	Treat burns, trauma and bleeding using leaves; treat arthritis using roots
I. wilsonii	roots and leaves	Clearing heat-toxin, detumescence, and removing toxic	Treat wind-heat headache, rhinitis, and mouth inflammation
I. kudingcha	leaves	Clearing heat-toxic, promoting fluid production, relieving high fever, moistening throat, removing phlegm, lowering pathogenic fire, and promoting blood circulation	The raw material of Large-leaved Kudingcha tea; anti-hypertension, anti-tumor, anti-aging, lowering blood pressure, lowing cholesterol, reducing blood fat, anti fatigue, protect cardiovascular system, antibiosis, and immuno-regulation
I. integra	leaves	Clearing heat-toxin, detoxication, and relieving pain	Broad-spectrum antimicrobial activities including bacteria, yeasts, and filamentous fungi
I. hainanensis	leaves	Clearing heat-toxin, promoting blood circulation, removing blood stasis, detumescence and relieving pain	The raw material of Shanlvcha tea, effectively used in hypertension, hyperlipidemia, high cholesterol, and coronary heart disease
I. angulata	leaves	Clearing heat-toxin, detoxication, and relieving pain	Treat hypertension, hyperlipidemia, high blood fat, mouth sores, sore throat, and inflammation
I .pentagona	leaves	Clearing heat-toxin, detoxication, relieving pain	Treat wind-heat headache, rhinitis, and mouth inflammation
I. corallina	leaves and roots	Clearing heat-toxic, promoting, blood circulation, and relieving pain	Treat burn injury, yellow ringworm, and muscle strain
I. franchetiana	leaves and roots	Clearing heat-toxic, dissipating phlegm, relieving cough, and astringing the lung	Treat hyperactivity cough, Nasal congestion, and asthma
I. godajam	barks	Removing toxic substance, eliminating carbuncles, and expelling rheumatism	Insect repellenting, relieving pain, treat ascariasis, and abdominal pain
I. paraguariensis	leaves	Yerba Mate tea, increasing energy, cleaning blood, and promoting perspiration	Burning fat, suppressing appetite, stimulating digestion, removing free radicals, enhancing memory, relieving pain, mildly laxative, and enhancing immunity
I. vomitoria	leaves	Yaupon tea	The raw material of Yaupon tea, anti-inflammatory and a antioxidants
I. glabra	leaves	Appalachian tea	The raw material of Appalachian tea containing caffeine alkaloid called mateine, a mildly stimulating relative of caffeine that tends not to produce side effects such as nervousness or sleeplessness
I. brevicuspis	leaves	Mate tea	Choleretic, antioxidant and intestinal propulsion activities and without central nervous system stimulant activity
I. guayusa	leaves	Amazon guayusa tea	Facilitate post–partum uterine healing

hypertension. The most popular species in *Ilex* L. of *non-camellia* teas in China is large-leaved Kudingcha botanically from *I. latifolia* and *I. kudingcha*. Large-leaved Kudingcha have enjoyed for about 2000 years of consumption in southern China due to various bioactivities: to quench thirst, refresh the mind, improve eyesight, and remove phlegm. Triterpenoids, flavonoids, and phenolic acids are the main metabolites from large-leaved Kudingcha that can protect cardiovascular system, anti-oxidation, anti-tumor, and regulate lipid metabolism. In South America, Yerba Mate (Paraguay tea) from *I. paragariensis* is widely-cultivated in the southern of South America (Paraguay, Argentina, Brazil, and Uruguay). It is used medicinally and as a natural, refreshing tea beverage since the time of the ancient Indians of Brazil, and Paraguay that "produced exhilaration and relief from fatigue" (Linck et al, 2014). In Argentina, Uruguay, Brazil and Paraguay, there is another species of "Mate": *I. brevicuspis* with a traditional use of choleretic, intestinal propulsion, and antioxidant activities (Filip and Ferraro, 2003). In the upper Amazon basin of Colombia, Ecuador, and Peru, *I. guayusa* can grow to an average of 10 m high and present a multitude of stems in 2 to 15 cm at breast height. Peru people consume the leaves from this plant as tea-like beverages for its medicinal qualities as "clean blood" (to remove excess sugars from the blood) to treat diabetes. It is also commonly used to reduce post-partum bleeding by cleaning the vagina after giving birth. In Ecuador, the folks also use guayusa to rinse their mouths and wipe the beverages on their arms, legs and face to keep skin from aging (Dueñas et al, 2016). In North America, especially the State of Texas, US, the Yaupon tea (leaves from *I. vomitoria*) is consumed to "attain ritual purity" due to its high antioxidant capability and regards to its positive effects on colon cancer cells (Wainwright and Putz, 2014). A species of evergreen holly, *I. glabra*, also known as Appalachian tea, dye-leaves, evergreen winterberry, gallberry, and inkberry, is native to the coastal plain of eastern North America, from Nova Scotia to Florida to Louisiana. Roasted and dried *I. glabra* leaves were first used by Native Americans to brew a black tea-like drink (Jaiswal et al, 2014).

4. Pharmacology of plants in *Ilex* L.

The plants of *Ilex* L. had been intensively studied in medicinal usage before 2000, especially for *I. chinensis*, *I. cornuta*, *I. asprella*, *I. pubescens*, *I. pernyi*, and *I. rotunda*. Afterwards it has been studied more in beverages: *I. latifolia*, *I. kudingcha*, *I.hainanensis*, *I. paraguariensis*, *I. brevicuspis*, *I. vomitoria*, and *I. glabra*. Those species exhibited a broad spectrum of biological and pharmacological activities.

4.1 Cardiovascular system protection and lipid metabolism activities

Species in *Ilex* L. have been used as traditional hypolipidaemic drugs for a long history. Consumption of these herbs improves serum lipid parameters in healthy dyslipidemic level and provides LDL-cholesterol reduction which can reduce the risk of cardiovascular diseases (De Morais et al, 2009). The aqueous extract from *I. pubescens* and *I. hainanesis*, can improve cardiac contractility, increase myocardial contractility and vasodilatation, reduce cardiac preload, afterload and myocardial oxygen reduction (Li et al, 2013). The triterpenoid-rich fraction from *I. hainansis* has the potential ability to regulate lipid metabolism and alleviate insulin resistance in high fat diet-fed rats (Cui et al, 2013). Ilexsaponin B (**65**), a triterpene saponin from *I. pubescens* and *I. asprella*, can reduce cholesterol levels and have the potential inhibition against xanthine oxidase activity in fat emulsion-fed dd-k mice (Zhou et al, 2013b). The roots of *I. rotunda* protect the cardiovascular system by reducing coronary flow and heart rate, improving hypoxia tolerance, and showing anti-arrhythmia and anti-myocardial ischemia bioactivities (He et al, 1997; Peng et al, 2014). Triterpenoid saponins from *I. cornuta* can protect H9c2 cardiomyocyte cells against H_2O_2-induced injury (Li et al, 2014b). The methanol extract of *I. pubescens* roots can prolong the bleeding time three fold and inhibit the generation of malondialdehyde released during the thrombin-induced platelet aggregation, in which ilexosides A−D and J are responsible for antithrombotic bioactivities (Kothiyal et al, 2012). *I. pubescens* extracts showed anti-platelet aggregation activity more significantly than aspirin by 36.55% and 27.30% at a dose of 10 μmol/L, respectively (Liu et al, 2008).

In vitro bioassays showed that the non-*Camellia* teas, especially Kudingcha and Yerba Mate can potentially reduce cardiovascular risk factors by regulating the lipid metabolism (Cardozo and Morand, 2016). Both *I. kudingcha* (Zheng et al, 2015) and *I. paraguariensis* (Bravo et al, 2014) appear as potent inhibitors against low-density lipoprotein (LDL) oxidation. Hyperlipidemic kunming mice could be reduced in the levels of blood glucose, plasma total cholesterol, and triglyceride after treated with *I. latifolia* and *I. paraguariensis* (Lu et al, 2012). Zheng et al (2015) also proved that Kudingcha can significantly reduce the SD rat in serum, liver lipid content and the liver fat wet weight. Chen and Wang (2012) reported that Kudingcha can significantly reduce TC, TG, LDL2C contents in serum of hyperlipidemic mice. The aqueous extracts of *I. paraguariensis* (AEIp) have the effects of mesenteric artery endothelium-dependent relaxation, leading the vascular endothelial to release nitric oxide (NO) or other metabolites in hypercholesterolemia mice model, and also it can stimulate the endothelial cells to release the vascular relaxing factor, resulting in the anti-hypertensive effect (Flores, 2006). Kudingcha leaf extracts can significantly decrease blood pressure in anesthetized dogs, and the abdominal subcutaneous adipose tissue index in obese rats and control, indicating that it has anti-hypertensive activities (Feng et al, 2015).

4.2 Antitumor activity

The species of *Ilex* L. showed the potential antitumor bioactivities. The aqueous extract of *I. pubescens* can improve

cytotoxicity of daunorubicin in the overexpression of P-170 leukemia cells *in vitro* (Ding et al, 2012). Jointly used with verapamil (VP), it can significantly increase the destruction ability of daunorubicin in K562/AO2 cells (Meng et al, 2007). *I. pubescens* can serve as a sensitizer of radiotherapy for nasopharyngeal carcinoma which relieves the side effects on the skin and gastrointestinal tract, pharyngeal mucosa in clinic (Zhou et al, 2014). Rotundic acid (**100**), a pentacyclic triterpenoid in *I. routunda*, *I. purpurea*, etc, has an anti-tumor activity in cell cycle progression and apoptosis. It can induce the apoptosis and G_0/G_1 cell cycle arrest of HepG2 cells which may be developed as a potential agent against hepatocellular carcinoma (Chen et al, 2013). Asprellic acids A (**15**) and C (**17**) from *I. asprella* can inhibit the growth of RPMI-7951 cell lines and KB cells, while asprellic acid B (**16**) can not (Kashiwada et al, 1993). Lipophilic extracts of *I. chinensis* leaves showed the strong inhibition activities against lymphocyte activation and proliferation in clinic (Li et al, 2012). Aqueous and ethanolic extracts of Yerba Mate can inhibit the development of normal colonic epithelium in human colon adenocarcinoma cell line HT29, which may be used in health promoting as a chemopreventive factor (Frant et al, 2012). Kudingcha at a concentration of 200 μg/mL, inhibited 75% TCA8113 cancer cells and significantly induced the apoptosis in TCA8113 cells by upregulating Bax, caspase-3, and caspase-9 expression, which demonstrated that Kudingcha has anti-cancer bioactivity *in vitro*. A study showed that Kudingcha could reduce the tumor size in the ICR mouse suffered from buccal mucosa cancer (Zhu et al, 2014). The extract of *I. paraguariens* has the chemopreventive activity by exhibiting a certain degree of cytotoxicity against the HepG2 cells and also by inhibiting the topoisomerases II (Ramirez-Mares et al, 2004).

4.3 Antioxidant and anti-inflammatory activities

The aqueous extract from *I. pubescens* can inhibit the connective tissue proliferation caused by salinities, confront mucosal epithelial necrosis, and inhibit inflammatory infiltration (Arbiser et al, 2005). Clinical experiments proved that the aqueous extract of *I. pubescens* can improve renal function in uremia stage or azotemia of patients (Haam and Fine, 1932). The ethyl acetate fraction of *I. latifolia* has significantly ferric reducing antioxidant power activity, DPPH radical scavenging activity and oxygen radical absorbance capacity. In addition, it has inhibition against NO production in macrophage RAW 264.7 cells, and cytotoxicity against human cervix carcinoma HeLa cells (Hu et al, 2014). Dicaffeoylquinic acids (diCQAs) from Yerba Mate can inhibit LPS-induced RAW 264.7 macrophage inflammation by suppressing NO/iNOS and PGE2/COX-2 pathways through inhibiting nucleus translocation of NF-κB subunits, p50 and p65 (Puangpraphant, 2012). The aqueous extracts of *I. kudingcha* can inhibit high-fat diet rat in hepatocytes lipid peroxidation as the dose-dependent manner within a certain concentration range, in which the polyphenol and flavonoid fractions were responsible for the antioxidant property (Sultana, 2011). Flavonoids from *I. centrochinensis* have the free radical scavenging and anti-inflammatory capacities, because their hydroxyl group at 4′-position of B-ring plays an important role (Li et al, 2015). *I. brevicuspis,* spreading in Argentina, has choleretic, antioxidant, and intestinal propulsion activities (Filip and Ferraro, 2003). The saponin-rich fraction from *I. pubescens* roots exhibits a suppressive effect on the histamine-induced acute paw edema in rats and can significantly elevate the tissue levels of anti-inflammatory cytokines of IL-4 and IL-10 (Wang et al, 2008a).

4.4 Anti-diabetic and anti-obesity activities

Consumption of both Kudingcha and Yerba Mate has improved the glycemic control and lipid profile of type II diabetes mellitus (T2DM) (Hao et al, 2013). Yerba Mate has the ability to decrease the differentiation of pre-adipocytes and to reduce the accumulation of lipids in adipocytes, leading to a low growth rate of adipose tissue and lower body weight in dietary-induced obesity animal models (Kang et al, 2012). The active components group (ACG) from *I. kudingcha* can significantly reduce the elevated levels of serum glycaemic and lipids of alloxan-induced T2DM (Song et al, 2012). The decoction of *I. asprella* roots can upregulate those lipid metabolism genes that cause chronic stress and hyperlipidemic fatty liver in male Wistar rats (Hu et al, 2012). The triterpenoid-rich fraction from *I. hainanensis* can alleviate insulin resistance associated with regulating PPARα and CYP2E1 expression in the liver of male Sprague-Dawley (SD) rats (Cui et al, 2013). Pedunculoside, an ester glucoside from the leaves of *I. rotunda* and *I. doniana*, showed a significantly hypocholesterolemic activity on hyperlipidemic albino rats (Zhao et al, 2015).

4.5 Anti-microbial activity

Methanolic and ethanolic extracts of Yerba Mate showed antimicrobial activity against food pathogens such as *Staphylococcus aureus*, *Listeria monocytogenes*, *Salmonella enteritidis*, and *Helicobacter pylori*, which reinforce the importance of Yerba Mate as a new natural antimicrobials (Martin et al, 2013). The aqueous extract of Yerba Mate (1000 mg/mL) also displays the inhibitory activity against a fungus species *Malassezia furfur* (Filip et al, 2010). The polarity extract of *I. cornuta* leaves contains the active compounds against *Candida albicans* and *C. glabrata* pathogenic fungi (Zgoda and Porter, 2001). Rotundic acid from *I. integra* fruits has a broad-spectrum antibacterial activity (Haraguchi et al, 1999).

4.6 Other activities

4.6.1 Intestinal propulsion activity

Bioassays showed that *I. brevicuspis* extracts could significantly increase bile flow (BF) in female Wistar rats within the first 30 min and the percentage of BF at 120 min. It

also produced an increase in the intestinal propulsion activity (Filip and Ferraro, 2003).

4.6.2 Anti-fertility activity

The extract of *I. cornuta* has the anti-pregnancy and anti-implantation in sc or ip injection. It can terminate each stage of pregnancy in alloxan-induced T2DM by exciting the uterus (Song et al, 2012). The total saponins of Kudingcha are responsible for exciting uterine smooth muscle of SD rats *in vitro* (He and Du, 2012). However, *I. guayusa*, a traditional Ecuadorian herbal medicine, is used to treat female infertility, and Contero et al (2015) verified that the ethanolic extracts from *I. guayusa* leaves have estrogenic activity in rats.

4.6.3 Anti-mitotic activity

Two paclitaxel analogues, 10-deacetylaxuyunnanine A and 7-(β-xylosyl)-10-deacetyltaxol C from the stem barks of *I. macrophylla*, showed the significant anti-mitotic activity and caused the bundling of microtubules (Roberge et al, 2000).

5. Discussion and prospective

Although 600 species of *Ilex* L. are distributed all over the world, only more than 40 species are used as medicines and teas, of which only about 20 species have been studied. It reveals that the species of *Ilex* L. need to be studied more in phytochemistry and pharmacology. In general, the medicinal parts of *Ilex* L. plants were derived from leaves, barks and root barks. Recent researches reported that the fruits of some species also can be used as medicines for human health, which promotes us to discover more components and their potential bioactivities from other parts of this genus plants.

Triterpenoids and triterpenoid saponins are the major constituents of the plants in *Ilex* L. responsible for various pharmacological activities. In addition, flavonoids, glycosides, pentyl esters, and other compounds have been also isolated from species of this genus. Different classes of compounds are responsible for different bioactivities, e.g., terpenoids and triterpenoid saponins for protection of the cardiovascular system and modulation of lipid metabolism activities, anti-inflammatory, anti-obesity, and anti-microbial bioactivities; flavonoids, polyphenols, and phenolic glycosides for the anti-cancer, anti-diabetic, anti-oxidant activities, etc.

Fortunately, quite a lot of species of *Ilex L.* have been used as not only folk medicines but also medicinal non-alcoholic beverages with a long history in eastern Asia, south and north America. To date, Kudingcha (*I. latifolia* and *I. kudingcha*), Yerba Mate tea (*I. paraguariensis* and *I. brevicuspis*), guayusa tea (*I. guayusa*), yaupon tea (*I. vomitoria*), and appalachian tea (*I. glabra*) have been paid more attention and popularly consumed in the world market due to their special flavors and medicinal values: prevention of several modern lifestyle- related diseases, such as the cardiovascular disease, obesity, diabetes, and cancer diseases. This beverages usage coincides with the theory of preventive treatment of diseases in TCM. So, the genus *Ilex* L. plays an irreplaceable role in preventing modern diseases in clinic.

Conflict of interest statement

All authors declare no conflicts of interest.

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